In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 13-215V

(Filed: September 1, 2017)

ALESSANDRA GIANNETTA,	*	To Be Published
Petitioner,	*	Meningococcal Vaccine; Menactra; Multiple Sclerosis ("MS"); Molecular Mimicry; Factual Dispute Regarding Onset; Entitlement to Compensation.
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Danielle Strait and Isaiah Kalinowski, Maglio Christopher and Toale, PA, Washington, D.C., for petitioner.
Jennifer Reynaud and Althea Davis, U.S. Dept. of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

A March 26, 2013, petition alleges that a meningococcal vaccination received on June 8, 2011, caused Alessandra Giannetta ("Ms. Giannetta" or "petitioner") to develop multiple sclerosis ("MS"). Petition at ¶ 2, 9.

An entitlement hearing was held on September 14-15, 2016, in Washington, D.C. After considering the record as a whole, and for the reasons explained below, I find that petitioner has sustained her burden in establishing causation. Furthermore, respondent has failed to put forth

[1] Because this ruling contains a reasoned explanation for my action in this case, it will be publicly available, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, I agree that the identified material fits within the requirements of that provision, I will delete such material from public access.

preponderant evidence that petitioner's MS was in fact caused by factors unrelated to the vaccines. Accordingly, petitioner is entitled to compensation.

I. Issues to be determined

The issues to be determined are: (1) when petitioner's first symptoms of multiple sclerosis occurred, and (2) whether the Menactra vaccination petitioner received on June 8, 2011, was the cause and/or trigger of her MS.

Petitioner alleges that the Menactra vaccine caused and/or triggered her MS, and that her symptoms began in July of 2011. Respondent disputes that the Menactra vaccine played any role in causing petitioner's condition, and further argues that petitioner's symptoms began in January of 2012. Respondent submits that petitioner "has not provided specific evidence showing that the Menactra vaccine can cause MS." Resp. Pre-Hearing Brief at 8. Specifically, respondent questions the legitimacy of Dr. Steinman's theory, stating that the best evidence for his theory "is a small study from 1981 where researches [sic] identified a single patient with antibodies against diphtheria toxoid in the spinal fluid." *Id*. at 9. Additionally, respondent cites to a lack of epidemiological support for Dr. Steinman's theory, noting that he "was unable to locate a study linking Menactra or any diphtheria toxoid-containing [vaccine] and MS." Respondent offers the testimony and expert reports of Dr. Soe S. Mar and Dr. Neal Halsey in support of his position.

II. Background

A. Procedural History

On March 26, 2013, Sandro and Nancy Giannetta ("Mr. Giannetta" and "Mrs. Giannetta") timely filed a petition for compensation on behalf of their then-minor child, Alessandra Giannetta, under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq*.[2] ("Vaccine Act" or "Program"). This case was initially assigned to now-Chief Special Master Dorsey. *See generally*, Petition, ECF No. 1; Notice of Assignment, ECF No. 2.

On September 27, 2013, respondent filed a Rule 4(c) Report ("Resp. Rpt.") indicating that he did not believe that this matter was appropriate for compensation. Resp. Rpt., ECF No. 21.

On October 15, 2014, petitioner submitted an expert report, a supplemental report, and a CV from Dr. Lawrence Steinman. Pet. Ex. 17, 18, 44; ECF Nos. 41, 80. Dr. Steinman is a neurologist at Stanford University. Tr. 78. He graduated from Dartmouth College with a major in physics and attended Harvard Medical School, where he focused on neurology and immunology. Tr. 78. He did a fellowship in neuroimmunology before completing his residency at Stanford, where he is now a professor of neurology, neurological sciences, pediatrics, and genetics. Tr. 79-80. Dr. Steinman is board certified in neurology. Tr. 79. He specializes in the immunological

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (1986). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

aspects of neurologic disease, and is considered an expert in MS. Tr. 80. He has published hundreds of articles on MS. Tr. 81.

Respondent filed expert reports and CVs from Dr. Soe Mar and Dr. Neal Halsey on February 4, 2014. Respondent's Exhibits ("Resp. Ex.") A-D, ECF No. 51. Dr. Mar is a pediatric neurologist. She attended the Institute of Medicine in Yangon, Myanmar from 1987 to 1988 and then attended the Royal College of Physicians and Surgeons. Tr. 177. She did her residency in England, then came to the United States to do fellowship training in pediatric neurology and genetics. Tr. 177. She has been a member of the faculty at Washington University in St. Louis since 2005, where she is currently an associate professor of neurology and pediatrics. Tr. 177; Resp. Ex. B at 1. Dr. Mar is board certified in pediatric neurology and neuroscience; she is the program director for the pediatric neurology residency program at St. Louis Children's Hospital, which is affiliated with Washington University School of Medicine. Tr. 178-79; Resp. Ex. B at 1. Dr. Mar specializes in pediatric CNS demyelinating diseases, including MS and acute disseminated encephalomyelitis ("ADEM"). Resp. Ex. A at 2. Dr. Mar teaches and supervises medical students, pediatric residents, pediatric neurology residents and fellows, and adult neurology residents in classrooms, conferences, journal clubs, and outpatient and inpatient settings. Resp. Ex. B at 1. Dr. Mar has never testified as an expert witness. Tr. 183-84.

Dr. Halsey is board-certified in pediatrics and pediatric infectious disease. Tr. 265. For the past 30 years, Dr. Halsey has conducted research on vaccines, vaccine preventable diseases, and vaccine safety. Resp. Ex. C at 1. He is currently the director of the Institute for Vaccine Safety at Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. Tr. 267. Dr. Halsey teaches medical students, pediatric residents, fellows, public health graduate students, and pediatricians about vaccines and vaccine safety. Resp. Ex. C at 1. He has published over 240 articles, mostly on vaccines and vaccine preventable diseases, and is a contributor on more than 100 policies on the use of vaccines for the Centers of Disease Control and the American Academy of Pediatrics. Tr. 270-71. Dr. Halsey also reviews papers for the New England Journal of Medicine, the Lancet, JAMA, Pediatric Infectious Disease Journal, and others. Tr. 271.

Dr. Halsey serves on various advisory committees responsible for making recommendations with regard to vaccine use and vaccine safety for the World Health Organization, Food and Drug Administration, the Centers for Disease Control and Prevention, and the American Academy of Pediatrics. Resp. Ex. C at 1. Dr. Halsey has served as a reviewer for vaccine safety reviews conducted by the Institute of Medicine, the American Academy of Pediatrics, and the Center for Disease Control and Prevention. *Id*. He was the chair of the Safety Review Committee for the Novartis quadrivalent meningococcal conjugate vaccine, Menveo, which is now on the market. Tr. 270. He also chaired a safety monitoring committee for studies of meningococcal B vaccine in Europe. Tr. 270; Resp. Ex. C at 1.

At hearing, Dr. Halsey conceded that Sanofi manufactures Menactra, and that, "three or four years ago," he was paid by Sanofi to serve as an expert to review issues with their vaccines. Tr. 312. He has also been involved in other endeavors where he has been paid by Sanofi, GlaxoSmithKline, Merck, and Kyron. Dr. Halsey stated the money he is paid goes to the university he works for, Johns Hopkins. Tr. 312-14.

Literature was submitted by both sides. Though not all of the articles are specifically mentioned, all were reviewed and considered in arriving at a decision in this matter. *See Moriarty v. Sec'y of Health & Human Servs*., 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision." (citing *Hazlehurst v. Sec'y of Health & Human Servs*., 604 F.3d 1343, 1352 (Fed. Cir. 2010))).

A status conference was held on February 26, 2015, at which time it was noted that the parties did not dispute that petitioner suffered from multiple sclerosis. Additionally, the Chief Special Master stated that "it is her view that the onset of [petitioner's] multiple sclerosis began on or around July 21, 2011, 43 days after vaccination." Order, ECF No. 57, at 1.

On June 11, 2015, Alessandra Giannetta ("Ms. Giannetta" or "petitioner") was substituted as petitioner.

This case was reassigned to me on October 19, 2015. ECF No. 74. A prehearing order was issued on November 23, 2015, setting a two-day entitlement hearing for September 14 and 15, 2016, in Washington, D.C. ECF No. 79.

A two-day hearing was held in Washington, D.C., on September 14 and 15, 2016. Alessandra Giannetta, Nancy Giannetta, and Sandro Giannetta testified as petitioner's fact witnesses. Dr. Lawrence Steinman testified as petitioner's expert witness. Dr. Soe Mar and Dr. Neal Halsey testified as respondent's expert witnesses. Post-hearing briefs were filed by both parties on November 21, 2016. ECF No. 104, 105.

B. Summary of the Medical Records

1. Petitioner's Health Prior to the Allegedly Causal Vaccination

Petitioner was born on November 3, 1996. Pet. Ex. 4 at 30. As a newborn, petitioner had jaundice, which resolved after a week of phototherapy. *Id*. at 31. Otherwise, she was a normal, healthy child, attaining developmental milestones at or before the expected dates. *Id*. at 31-32. Petitioner had frequent ear infections as an infant and was treated with tubes at 10 1/2 months. *Id*. at 32. Additionally, she had a tonsillectomy when she was in fourth grade. *Id*.; *see also* Pet. Ex. 3 at 9-11. Petitioner was also diagnosed with asthma as a young child; however, she has not had any symptoms since then. Pet. Ex. 5 at 59.

Petitioner was a very active teenager, involved in gymnastics and cheerleading. Pet. Ex. 4 at 32; Tr. 8. On January 17, 2011, she presented to East Bank Chiropractic Health Center ("East Bank"), complaining of "dull, aching, tightness, [and] discomfort" as well as pain in her upper and middle back and between her shoulder blades while doing gymnastics. Pet. Ex. 1 at 2. The exam "revealed a significant decrease of normal range of motion in…right cervical rotation and left lateral lumbar flexion….Palpation of the muscles revealed spasm in…right upper thoracic area, right mid thoracic area and right lower thoracic area." *Id*. It was noted by the chiropractor that there was no change after adjustment. According to the chiropractor, this meant that there was "a 60% chance of a need for long-term treatment" as well as "a 60 to 80% chance of long-term

residuals of [petitioner's] primary presenting musculoskeletal, orthopedic and neurological complaints." *Id*.

A month later, on February 14, 2011, petitioner returned to East Bank "complaining of discomfort and or paresthesia in the following areas: cervical, mid thoracic, lower thoracic, lumbar and sacral." Pet. Ex. 1 at 3. She was noted to have "[m]ultiple subluxations with spasm, hypomobility and end point tenderness." *Id*. Adjustments were performed on her cervical, thoracic, lumbar, and sacral spine. *Id*. The assessment remained "a 60% chance of a need for long-term treatment" and "a 60 to 80% chance of long-term residuals…." *Id*. The "goals of continued treatment" were to "decrease segmental dysfunction, decrease swelling and inflammation, decrease muscle spasms, corrective care, increase proprioception, increase function, keep the patient working, [and] arrestment of degeneration and surgical avoidance." *Id*.

2. Petitioner's Health After the Menactra Vaccine

On June 8, 2011, petitioner, then 14 and one-half years old, presented to her primary care provider ("PCP"), Dr. Bharti Amin, for a sports physical for school. Pet. Ex. 3 at 5. She was noted to be a well child with some scoliosis. She was administered the Menactra vaccine. *Id*.

On August 1, 2011, petitioner presented to the emergency room at Franciscan St. Margaret ("Franciscan"), complaining of numbness and tingling in her right foot and leg that had been ongoing for one week. Pet. Ex. 11 at 6, 8. Petitioner also complained of lower back pain. *Id*. at 9. An x-ray of petitioner's lumbar spine showed scoliosis, but was otherwise normal. *Id*. at 11.

Shortly thereafter, in early August of 2011, petitioner had an appointment with a neurologist who would not see her when she arrived because he did not treat patients younger than 18. Pet. Ex. 12 at 4.

On August 11, 2011, petitioner presented to a chiropractor at Lansing Chiropractic Clinic ("Lansing"), complaining of right foot, ankle, and leg numbness for three weeks. Pet. Ex. 6 at 3. She was taking Claritin and Benadryl. *Id*. at 4. She was involved in cheerleading and tumbling. *Id*. Petitioner advised that the numbness and tingling started in her foot weeks ago and moved up to her leg and thigh. *Id*. at 12. She also complained of lower back pain. *Id*. It was noted that petitioner had been seen at the E.R. at Franciscan where she underwent x-rays which showed a curvature in her spine. *Id*. It was also noted that petitioner went to a neurologist, who would not see her. *Id*.

An MRI of petitioner's lumbosacral spine was performed on August 12, 2011, to rule out lumbar nerve root impingement. Pet. Ex. 13 at 7. The impression was

> Lumbar rotatory levoscoliosis not adequately characterized on the supine axial and sagittal sequences. Findings consistent with fatty infiltration of the filum terminale without significant thickening. Although this can be a normal variant, this has also be [sic] described in association with tethered cord syndrome[3] and clinical

[3] The spinal cord normally floats freely inside the spinal canal. With tethered cord syndrome, tissue attachments limit the movement of the spinal cord, causing abnormal stretching of the cord.

> correlation is recommended….Normal appearance of the disc spaces without protrusion, canal or foraminal stenosis.

Id.

Petitioner was seen at Lansing on August 12, 2011, October 14, 2011, November 2, 2011, November 9, 2011, and November 11, 2011 with no change noted. Pet. Ex. 6 at 11.

Petitioner next presented to her PCP on January 24, 2012, with three weeks of "right hand tingling, even wrist, feels weak, gets same in left, mom said walked like tripping x 1 (did not fall), was in the car talking to mom and slurred speech. In summer felt same in one leg." Pet. Ex. 3 at 5. The assessment was "migraine?? (??demyelinating disease) [sic]." *Id*.

A brain MRI performed on January 25, 2012, showed "multiple, ovoid and rounded T2/FLAIR hyperintensities within the supratentorial white matter… greater than 15 periventricular and several scattered subcortical foci." Pet. Ex. 13 at 3. The MRI was limited due to petitioner's braces, but showed "[m]ultifocal, periventricular and juxtacortical white matter signal changes. The pattern and distribution is highly suspicious for a demyelinating process such as multiple sclerosis…." *Id*.

On January 26, 2012, petitioner presented to the pediatric neurology department at the University of Chicago Medical Center ("Chicago") with numbness on the left side of her face and in her right hand ongoing for one month. Pet. Ex. 5 at 66. Petitioner gave the neurologist a detailed medical history, describing an episode of numbness in her left foot and calf in July of 2011 which lasted for one month but resolved on its own, as well as an episode of blurred vision occurring two months ago which lasted for one week before resolving on its own. *Id*. Petitioner also informed the neurologist that she had previously received a referral to a neurologist but could not get an appointment. *Id*. One day prior to her presentation, she had a terrible headache for which she took Advil without improvement. *Id*. at 67. She also complained of chronic lower back pain which worsened with exertion but did not prevent her from participating in cheerleading and gymnastics. *Id*. It was noted that petitioner's mother had an extensive medical history of symptoms beginning at age 37, including chronic migraines, memory loss, numbness, confusion, ADHD, anxiety, ulcers, and brain lesions. *Id*.

Petitioner's labs showed a positive ANA; a lumbar puncture showed five oligoclonal bands in the cerebrospinal fluid. Pet. Ex. 5 at 70. An MRI of petitioner's brain and spine showed multiple white matter lesions in the brain, but no lesions in the spine. *Id*. Multiple sclerosis was thought to be the most likely diagnosis. *Id*. Since petitioner was not experiencing any limitations in her daily life at that point, the pediatric neurologist and a specialist in adult MS decided that no intervention was necessary. *Id*.

On February 13, 2012, petitioner presented to the Child & Adolescent Neurology Department at the Mayo Clinic ("Mayo") with "white matter disease." Pet. Ex. 4 at 30. It was

---

Tethered Spinal Cord Syndrome, American Association of Neurological Surgeons, aans.org (last visited July 28, 2017).

noted that petitioner had an episode in the summer of 2011 which may have represented demyelination, but there was no definite evidence to support that. *Id*. at 34. The more recent symptoms occurring within the last four to six weeks were consistent with demyelinating disease, as was the MRI of the brain. *Id*. The presence of oligoclonal bands in the cerebrospinal fluid further bolstered the likelihood that petitioner had a demyelinating disease. *Id*. Additional tests were ordered. *Id*.

On February 16, 2012, petitioner presented to Mayo for an "MS subspecialty consultation." Pet. Ex. 4 at 11. It was noted that petitioner had an upper respiratory infection prior to a July 2011 episode of numbness in her foot and leg, which lasted about a month and resolved on its own. *Id*. Recent tests revealed "at least two new lesions are seen in our own scans, and there are at least five to eight of these that are enhancing as a result of gadolinium enhancement, so she clearly has very active disease….She also has lesions at the level of the cervical thoracic spine. Most prominently, it is at the level of T10 on the right-hand side…." *Id*. Petitioner's "neurological history and examination were compatible with diagnosis of probable multiple sclerosis. The fact is that the patient has had two independent events…[and] multiple MRI scans, all of which show an increased number of lesions. Many of these are enhancing. All support a diagnosis of multiple sclerosis." *Id*. at 12. Petitioner was diagnosed with relapsing-remitting multiple sclerosis, and interferon therapy was recommended. *Id*.

That same day, petitioner saw another specialist, who noted the following:

> She was in good health until July 2011 when she experienced an upper respiratory illness associated with nasal congestion, and then about a week later, she noticed numbness in the right leg. It began in the toes and ascended to just distal to the knee over the course of a few days to weeks. The symptoms lasted a month and resolved on their own….She had no trouble with walking or running at that time. Then in mid-January 2012, she developed numbness involving the left face and right hand. She noticed her handwriting was affected. She developed blurred vision for a few days, not associated with eye pain or changes in color vision. On several occasions, she would slur her speech, but this was very brief. These symptoms evolved over several days and then persisted for about a month.

Pet. Ex. 4 at 8.

Additionally, it was noted:

> [F]amily history is significant in that her mother does have some lesions in the brain which she reports have been thought to potentially be related to MS. Her primary difficulty is cognitive impairments and migraines as well as mood disorder. This has been evaluated in Arizona, and she was not given a definitive diagnosis at the time. There is no other family history of MS or autoimmune disease.

Id. The impression was that petitioner "has had two attacks which sound rather typical for attacks associated with multiple sclerosis." *Id*. at 10.

Petitioner presented to Chicago on March 18, 2012, for a follow-up for MS. Pet. Ex. 5 at 63. It was noted that the "patient also reported a 1 month history of right leg numbness and tingling 6 months prior to this admission, which resolved spontaneously. Patient denied any prior fever, altered metal status or any particular URI symptoms prior to this admission….She was unclear about prior vaccination before symptom onset." *Id*. The assessment was

> [W]hite matter lesion. This could represent clinically isolated syndrome versus multiple sclerosis or ADEM. We will repeat brain MRI and whole spine MRI with and without contrast in 3 months. Patient's parents hope that MRI can be scheduled after patient's dental braces are removed in 2 months. We may consider repeating CSF studies in 3 months to assess interval change of her oligoclonal band profile. The patient is instructed to start vitamin D supplementation (2000 mg p.o. daily). We will follow up with the patient in 3 months.

Id. at 64.

Petitioner presented to Chicago on April 2, 2012, complaining that she woke with numbness on her right side. Pet. Ex. 7 at 4. She did not report weakness or dysphagia. *Id*. Petitioner was prescribed Avonex and advised to hydrate and take vitamin D supplements. *Id*. at 5.

Over the next several months, petitioner continued to be symptomatic. She was prescribed various medications, but continued to experience symptoms. *See generally* Pet. Ex. 5, 16. In December of 2012, petitioner was prescribed Tysabri by infusion. She continues to treat with Tysabri. *See generally* Pet. Ex. 16.

C. Affidavits and Testimony at Hearing

1. Affidavit and Testimony of Petitioner Alessandra Giannetta

Petitioner testified that she was diagnosed with scoliosis in middle school after experiencing sharp pains in her lower back. Tr. 8. As a teenager, she was active in cheerleading and gymnastics, which caused her to have back pain. Tr. 8-9. According to petitioner, she went to the chiropractor for her back pain; she also took Tylenol and iced her back. Tr. 8. The chiropractor would adjust her back and the pain would subside for a couple of hours, but then it would come back. Tr. 9; Pet. Ex. 55 at 1-3. Petitioner did not recall any episodes of numbness or tingling prior to receiving the meningococcal vaccine and being diagnosed with multiple sclerosis. Tr. 10; Pet. Ex. 55 at 2. She no longer has bad back pain because she no longer participates in sports. Tr. 9.

Petitioner testified that she recalled the summer of 2011 when she received the meningitis vaccine. Tr. 10; Pet. Ex. 55 at 2. She recounted that during the week of July 4, 2011, she and her family were at their lake house when her foot became numb. Tr. 12. She told her parents that her foot was numb and was told that her foot must have fallen asleep, and that it would get better in a few hours. Tr. 12 -13. The numbness did not get better, and over the next few days it progressed up her leg. Tr. 13. Petitioner did not recall seeing a doctor at that time. Tr. 13-14. She recalled going to the chiropractor that summer and being treated for her back because the chiropractor thought the numbness was coming from her back. Tr. 15, 17-18; Pet. Ex. 55 at 2. Petitioner recalled

going to the emergency room and having an MRI and x-rays of her lower back, but did not recall the results. Tr. 15. The leg numbness lasted about a month, and then she woke up one morning and it was gone. Tr. 17-18; Pet. Ex. 55 at 2.

Petitioner testified to having a stuffy nose for about a month during the summer of 2011 that was treated with over-the-counter medication and then a medication she could not recall that was prescribed by the doctor. Tr. 16-17. Petitioner stated that she had had similar stuffy nose symptoms in the past, maybe once a year. Tr. 30-31. She did not recall ever being given a diagnosis of non-allergic rhinitis. Tr. 32.

Petitioner stated that in the late fall of 2011, she had episodes of numbness and fatigue in her hands, issues with her writing ability, blurry vision, and slurred speech which came and went. Tr. 19; Pet. Ex. 55 at 2. She stated that she told her mother about these episodes when she came home from school. Tr. 19. She did not recall anything else during that semester. Tr. 20.

Petitioner described an episode of slurred speech while in the car with her mother going to a basketball game. Tr. 20-21. She recalled seeing her pediatrician, who sent her to a neurologist, who would not see her because she was under 18. Tr. 21. She went to the University of Chicago "a week or two later" and was admitted for a few days. Tr. 21-22. She recalled having a lumbar puncture, an MRI, and an evoked potential test. Tr. 23. The doctors asked her about her history and whether she had recently had any vaccinations or been sick; petitioner told them that she had received the meningitis vaccine. Tr. 23. She was not given a definitive diagnosis at that time, but the doctors suspected that she had multiple sclerosis. Tr. 23-24; Pet. Ex. 55 at 2.

Petitioner stated that she then went to the Mayo Clinic; similar tests were done there, and she was diagnosed with multiple sclerosis. Tr. 24-25. Petitioner did not begin treatment, because at that time she was not having any symptoms of MS. Tr. 25.

Petitioner testified that she was fine until Thanksgiving, when her legs became numb but unlike the summer of 2011, the numbness spread up her legs very quickly and she had severe pain. Tr. 25-26. Dr. Javed, her neurologist from Chicago, prescribed prednisone and then Avonex shots once a week, which she received for about a year. Tr. 26-27. According to petitioner, the Avonex did not work; she kept having relapses and would have to take increased doses of prednisone, which seemed to help. Tr. 27-28.

Petitioner stated that she has been on Tysabri for the past several years; it seems to be working. Tr. 28. Her last relapse was a year before the hearing. Tr. 28. Petitioner explained that a relapse usually involves numbness of her right leg or right hand. Tr. 28. When asked to compare the numbness in her leg in July of 2011 to what she experiences during relapses, petitioner said it is pretty much the same; the numbness will start in her foot and go up her leg, but if it starts in her hand, it stays in her hand. Tr. 31. She confirmed that she had never had symptoms like that before July of 2011. Tr. 31-32.

Petitioner stated that after her diagnosis, she had to quit sports because the coaches were concerned about possible relapses. Tr. 29. She is now in college at Ball State University. Tr. 29;

Pet. Ex. 55 at 2-3. She does not like to talk about her MS. Tr. 30. Her mom made her see a psychiatrist because she thought petitioner was angry. Tr. 30.

2. Affidavit and Testimony of Petitioner's Mother, Nancy Giannetta

Nancy Giannetta is petitioner's biological mother. Tr. 49. According to Mrs. Giannetta, petitioner was a healthy, active teenager who had back problems related to sports. Pet. Ex. 56 at 1. The pediatrician diagnosed petitioner with scoliosis. *Id*.; Tr. 50. Prior to the summer of 2011, petitioner was taken to chiropractors for back pain resulting from tumbling and gymnastics; the chiropractor suggested that petitioner quit those sports. Tr. 50.

Mrs. Giannetta testified that she would accompany petitioner to medical appointments and was with petitioner at her high school physical on June 8, 2011, the day she received Menactra vaccine. Pet. Ex. 56 at 1; Tr. 50-51. She was deemed a healthy teenager on that date. Tr. 51-52.

Mrs. Giannetta recalled that in July of 2011, petitioner began complaining that her foot was numb and then later that her leg was numb. Tr. 53. Mrs. Giannetta clarified that she was taking Topamax at the time for very severe migraines which caused some memory issues. Tr. 53. She remembered petitioner going to the ER for the leg numbness, and that the pediatrician gave her a referral to a neurologist, Dr. Bhasin, who refused to see petitioner when she arrived because she was a minor and he only treated adults. Tr. 56-57; Pet. Ex. 56 at 1. Mrs. Giannetta recalled that, when she took petitioner to the appointment and Dr. Bhasin refused to see her because he did not treat children, she became upset and the situation "got heated." Tr. 56-57.

On cross examination, Mrs. Giannetta was questioned about the record from Dr. Bhasin's office, which is dated 2013 and states that petitioner was not seen because she was under 18. Tr. 71. Mrs. Giannetta stated that the date on the document was wrong; she explained that she remembered that it was 2012 because one of their cars was stolen at the same time. Tr. 71-72; Pet. Ex. 12 at 4. Mrs. Giannetta explained that she went to Dr. Bhasin's office in 2013 to get them to write a note confirming that petitioner had been there but was not seen due to her age.[4] Tr. 76.

Mrs. Giannetta stated that after being turned away from the neurologist's office, she was outside of her home that evening and spoke to her neighbor, who was a chiropractor. Tr. 57-58. She explained petitioner's complaint of numbness in her leg and her neighbor said to bring petitioner to him [at Lansing Chiropractic], he could fix the problem. Tr. 58. Mrs. Giannetta brought petitioner to Lansing multiple times, but it did not help. Tr. 60. She could not remember what happened with petitioner's numbness after that because she was dealing with her own migraines. Tr. 60; Pet. Ex. 56 at 2.

According to Mrs. Giannetta, petitioner was a freshman in high school during the fall of 2011. She recalled petitioner's complaints of blurred vision, that she couldn't write that day, or she had slurred speech various times that fall. Tr. 61. Mrs. Giannetta stated that she always intended to call the doctor in the morning, but then she would forget. Tr. 61; Pet. Ex. 56 at 2. Mrs.

[4] Based on the content of Mrs. Giannetta's testimony, it is found that she mistakenly testified to the year being 2012 rather than 2011.

Giannetta recalled five or six times between September and January that petitioner made complaints of numbness in her leg or hand, or difficulty writing. Tr. 74.

Mrs. Giannetta recounted an incident in January of 2012, when she heard petitioner slurring her speech in the car. Tr. 61-62. Mrs. Giannetta called Dr. Amin, who was out of town. Tr. 62. She started calling around for a neurologist, because the symptoms that petitioner was complaining of were similar to the symptoms that Mrs. Giannetta experiences with her migraines, so she thought that petitioner might have a neurological issue. Tr. 62. She made an appointment at the University of Chicago. Tr. 62. Dr. Amin saw petitioner first and ordered an MRI. Tr. 62-63. Then they went to the University of Chicago, where Dr. Silver reviewed the MRI and told them that there were eleven lesions on petitioner's brain. Tr. 63. Dr. Silver brought in Dr. Kohrman and petitioner was admitted. Tr. 64. Mrs. Giannetta recalled that Dr. Kohrman specifically asked if petitioner had received the meningitis vaccine. Tr. 72. Mrs. Giannetta stated that after that, she began doing research, and put together the connection between the Menactra vaccine and the MS. Tr. 72. She stated that she also told Dr. Javed about the meningitis vaccine, but he was more focused on treating petitioner's MS than trying to identify a cause. Tr. 73; Pet. Ex. 56 at 2. Additional tests were done and the doctors suspected that petitioner had MS, but she was discharged without a definitive diagnosis. Tr. 65. They were referred to Dr. Javed, but could not get an appointment until March, so Mrs. Giannetta took petitioner to the Mayo Clinic. Tr. 65-66.

Mrs. Giannetta recalled that she took petitioner to the Mayo Clinic around Valentine's Day. Tr. 66. The doctors at Mayo did tests and asked about petitioner's symptoms from the summer of 2011 before rendering a diagnosis. Tr. 66-68. The doctors discussed putting her on Rebif, but Mrs. Giannetta thought it was too harsh, so they opted to not do anything at that point because petitioner was not having symptoms. Tr. 67.

Mrs. Giannetta recalled taking petitioner to Dr. Javed again around Thanksgiving when petitioner had a relapse of tingling and numbness in her legs and her arm. Tr. 68-69. Petitioner was prescribed prednisone, which did not help. Tr. 68-69. Petitioner was then prescribed Tysabri, which she has been taking for two and half years. Tr. 69.

3. Affidavit and Testimony of Petitioner's Father, Sandro Giannetta

Sandro Giannetta is petitioner's biological father. Tr. 34. According to Mr. Giannetta, petitioner was a healthy child; she had colds, ear infections requiring tubes, and a tonsillectomy. Tr. 34-35. As a teenager, petitioner had scoliosis and complained of back pain. Tr. 35-36. According to Mr. Giannetta, his wife was mostly responsible for petitioner's pediatric visits but she would call him after the appointments to tell him "that it went okay." Tr. 35.

Mr. Giannetta stated that petitioner was involved in cheerleading, tumbling, gymnastics, and soccer. Tr. 36. He did not recall petitioner having injuries from sports, but she did have back pain. Tr. 36. She would go to the chiropractor, who would adjust her back, but the adjustments would only last for a day or two. Tr. 36.

Mr. Giannetta did not remember dates very well, but believed that petitioner received the vaccine in June of 2011 and the numbness started in July when they were on vacation. Tr. 45. He

recalled that petitioner had a cold for a long time after receiving the Menactra vaccine. Tr. 37-38. She also complained that her leg was numb. Tr. 37-38. He remembered petitioner punching her leg to show him that her leg was numb; after that, he took her to the emergency room at Franciscan. Tr. 38-39. Mr. Giannetta did not recall what tests the doctors ordered, or what their conclusions were. Tr. 39-40. He did remember that, after the ER visit, a neighbor who was a chiropractor said he could treat the numbness in petitioner's leg. The chiropractic adjustments worked for a day and then petitioner's symptoms came back. Tr. 40-41.

In his affidavit, Mr. Giannetta stated that petitioner made "vague complaints about odd symptoms" through the fall of 2011. Pet. Ex. 57 at 2. At hearing, he explained that petitioner had "sniffles…more than normal," and that she was complaining about numbness and tingling in her leg, which caused her to quit cheerleading – she did not finish out the year. Tr. 47.

Mr. Giannetta remembered his wife taking petitioner to the University of Chicago and calling him to tell him petitioner was being admitted. Tr. 41-42. He recalled one of the doctors asking if petitioner had any recent vaccinations. Tr. 42. Mrs. Giannetta answered the doctors' questions, but Mr. Giannetta did not recall what the answers were. Tr. 42-43. According to Mr. Giannetta, petitioner was still experiencing numbness and tingling in her right leg at that time. Tr. 42. After seeing the doctors at Chicago, Mrs. Giannetta took petitioner to the Mayo Clinic, where she was diagnosed with MS. Tr. 43. Mr. Giannetta estimated that petitioner has had four or five relapses since being diagnosed with MS. Tr. 43. Her MS is being treated with Tysabri; if petitioner misses a dose of Tysabri, she will experience numbness and tingling. Tr. 43.

III. Onset of MS Symptoms

The parties in this case presented highly qualified experts. Dr. Steinman and Dr. Mar debated the issue of onset of petitioner's multiple sclerosis. The experts agreed that, as of the end of January of 2012, petitioner had multiple sclerosis, and this diagnosis was confirmed by an MRI performed on January 25, 2012 which showed "multiple, ovoid and rounded T2/FLAIR hyperintensities within the supratentorial white matter" and "greater than 15 periventricular and several scattered subcortical foci," as well as a lumbar puncture showing five oligloclonal bands. Pet. Ex. 13 at 3.

Dr. Steinman placed onset in July of 2011, between 43 and 47 days after the vaccination. Tr. 137; Pet. Ex. 17 at 4; Pet. Ex. 44 at 1-3. Dr. Mar placed onset in January of 2012. Tr. 203; Resp. Ex. A at 5.

A. Diagnostic Criteria of MS

Drs. Steinman and Mar agreed that the McDonald diagnostic criteria help define the clinical radiological criteria for making a diagnosis of MS. Tr. 98. It is used for both adults and children. Tr. 186-87. Dr. Mar explained that, for children older than age 12, it has been modified to rule out encephalopathy. Tr. 187. For children under 12, there are more modifications due to

other demyelinating diseases that can mimic MS, such as neuromyelitis optica ("NMO"), ADEM, vasculitis, NMDA receptor encephalitis, and other immune diseases. [5] Tr. 186-88.

According to Dr. Steinman, it is difficult to say how or at what age MS develops. However, most patients are diagnosed after the age of 18. Tr. 96-97. Additionally, MS has many manifestations, including motor and/or sensory problems, balance and/or coordination problems, and even personality or vision problems. Tr. 94-95. A hundred genes are associated with MS, which may influence how a person's symptoms present. Tr. 95. Both Drs. Steinman and Mar agreed that MS is diagnosed by taking a history, doing an examination, and conducting tests. Tr. 101; 188. They also agreed that MS can present with a variety of clinical symptoms, and that the pathological process can begin before clinical symptoms manifest. Tr. 233. Additionally, Dr. Mar pointed out that there can be clinical symptoms with a normal initial MRI; demyelination can develop later. However, radiological evidence alone is not sufficient to diagnose MS. Tr. 232. Dr. Mar explained that a person with demyelinating lesions but no symptoms will not be diagnosed with MS. Tr. 232-33.

Dr. Steinman stated that oligoclonal bands, which are detected on a test called electrophoresis, are a "key aspect" in the laboratory analysis and pathology of suspected MS. Pet. Ex. 17 at 7. Though the exact role of the specific antibody responses in the central nervous system is unknown, it is clear that the vast majority of conditions where oligoclonal bands are detected in the cerebrospinal fluid ("CSF") are neuroinflammatory conditions. *Id*.; Tr. 151. Dr. Steinman noted that petitioner had five oligoclonal bands of immunoglobulin in her CSF in January of 2012. Pet. Ex. 17 at 7. Dr. Mar added that while the presence of oligoclonal bands can support a diagnosis of MS, they are not diagnostic alone; a clinical attack is necessary to meet the McDonald criteria. Tr. 240-41.

Both Drs. Steinman and Mar agreed that a diagnosis of MS by the McDonald criteria requires "dissemination in time and space" of symptoms. Otherwise, it is referred to as "clinically isolated syndrome." Tr. 133, 240-41, 254. The first clinical attack would be described as a clinically isolated syndrome, or "acute," because it is unknown whether the symptoms will recur or whether it was an isolated event. Tr. 133, 236-37. A child is not given a diagnosis of MS until he or she has symptoms which repeatedly recur. Tr. 238. Dr. Mar stated that about 98 percent of pediatric MS cases are relapsing-remitting MS, which means that the child has acute symptoms, then recovers; almost 100 percent of children with relapsing-remitting MS will have another attack. Tr. 188. Additionally, pediatric onset MS tends to be more aggressive than adult onset MS; in the first two years after the diagnosis, children tend to have more frequent relapses. Tr. 189.

Dr. Mar agreed that the updated McDonald criteria of 2010 allows for a diagnosis of MS with only one episode of symptoms, or "clinical attack," as long as certain radiological evidence is present. Tr. 235-38.

[5] Tip Sheet Revised McDonald Diagnostic Criteria for MS, National Multiple Sclerosis Society (2010), nationalmssociety.org

B. The Experts' Opinions on Onset

Dr. Steinman placed the first manifestation of petitioner's MS in July of 2011, 42 to 47 days after the June 8, 2011 Menactra vaccine. Tr. 123-24. He based his opinion upon petitioner's description of progressive numbness in her leg in July of 2011, combined with later episodes of numbness. Tr. 123-24.

Dr. Steinman testified that petitioner distinguished the numbness in her leg that she experienced in July of 2011 from the low back pain for which she previously received chiropractic manipulation in early 2011. Tr. 123. Dr. Steinman noted petitioner's testimony describing her symptoms after her diagnosis of MS as similar to the leg numbness that she experienced in July of 2011. Tr. 124. Dr. Steinman stated that what petitioner described in July was "very new and very consistent" with initial manifestations of MS. Tr. 125. To that end, Dr. Steinman pointed to Dr. Javed's records in which petitioner described not being able to feel her leg[6] as a "profound and eloquent description" of something that in hindsight was very serious. Tr. 106-07.

Dr. Mar opined that, based on the history and exam in the medical records, the symptoms that petitioner presented with in July of 2011 were not consistent with a demyelinating attack. Tr. 211. Instead, Dr. Mar attributed petitioner's numbness and tingling during July of 2011 to her participation in "high impact sports," which put her at risk for "discomfort/pain and sensory symptoms." Resp. Ex. A at 5. Dr. Mar referenced the Lansing chiropractic records from August of 2011, pointing to the dermatomes[7] in a diagram and stating that petitioner had hypoesthesia[8] on the right at L3-4, L5, and S1. Tr. 203-04. Dr. Mar explained that dermatomal involvement indicates that the hypoesthesia is coming from the spinal root, spinal cord, or nerve plexus – sources outside of the central nervous system. Tr. 211-12. According to Dr. Mar, based on the fact that petitioner had only partial numbness following the dermatomal pattern as described in the diagram, it is more likely that the numbness was coming from that single spinal root rather than the brain. Tr. 204-08, 212-14; Pet. Ex. 2 at 13. MS is a disease of the central nervous system; the chiropractic records point to a problem in the peripheral nervous system. Tr. 212. Therefore, petitioner's symptoms were not consistent with a demyelinating attack. Tr. 211.

Dr. Mar noted that an MRI of petitioner's lumbosacral spine taken on August 12, 2011, did not show demyelination, but agreed that there can be clinical symptoms with an initially normal MRI; demyelination can develop later. Resp. Ex. A at 5; Tr. 233. Dr. Mar pointed out that petitioner complained of pain, tightness, and discomfort in January and February of 2011, but noted that "there was no good neurological documentation" at that time; therefore, the symptoms could have resulted from petitioner's tumbling. Tr. 214. However, Dr. Mar submitted that

[6] Dr. Javed refers to petitioner not being able to feel her left leg, but all other records, refer to numbness in her right leg. Tr. 106-07; Pet. Ex. 7 at 8. Dr. Steinman explained that, due to the use of electronic medical records, "it just takes one mistake and then the mistake gets propagated"– the patient's medical history is imputed to each visit, repeating the mistake continuously. Tr. 125.

[7] A dermatome is an area of skin supplied with nerves from a single spinal nerve. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (32nd ed. 2012) at 497, hereinafter "*Dorland's*."

[8] Hypoesthesia is abnormally decreased sensitivity. *Dorland's* at 901.

petitioner's symptoms could have been signs of transverse myelitis, another symptom of MS which can present as numbness and tingling, but there was not enough information in the records to know. Tr. 214.

Dr. Steinman testified that he distinguished petitioner's complaints of lower back pain in January of 2011 from her complaints of numbness in July of 2011 by filtering his interpretation through the eyes of a neurologist rather than that of a chiropractor, noting that there was no evidence that petitioner had any neurological complaints before July of 2011. Tr. 125-26.

Dr. Steinman added that petitioner was a very active, social girl who participated in gymnastics, tumbling, and cheerleading. Tr. 123. Other than preexisting scoliosis, she was a healthy child. Tr. 123. He also noted that in July of 2011 she had several weeks of "sniffles," which was of little significance. Tr. 123.

In Dr. Steinman's opinion, petitioner had dissemination in time and space, radiological evidence, and oligoclonal bands, in January of 2012, which, in addition to some pediatric criteria, satisfied the McDonald criteria. Tr. 131-32. He added that when petitioner went to Mayo the following month, she had MS. However, because it was her first time presenting to Mayo, she was diagnosed with "clinically isolated syndrome." Tr. 134-35. Dr. Mar agreed that petitioner's MRIs in January and February of 2012 confirmed a diagnosis of MS. Tr. 232.

In support of her opinion that petitioner's MS began in January of 2012, Dr. Mar referenced Dr. Silver's notes at Chicago in January of 2012 and Dr. Patterson's notes at Mayo in February of 2012, pointing out that there was nothing definitive in the events of July of 2011 to indicate demyelinating disease. Tr. 199-202. According to Dr. Mar, Dr. Patterson is a very well respected pediatric neurologist; he is an astute clinician and very thorough. Tr. 202-03. Dr. Patterson looked at petitioner's history and, based on petitioner's MRIs, determined that the first attack was in January of 2012; that is why he diagnosed petitioner with clinically isolated syndrome. Tr. 199-202, 210-11; Pet. Ex. 4 at 34; Pet. Ex. 5 at 25, 66.

Dr. Steinman countered by referencing the Mayo Clinic record from February of 2012, which stated that petitioner "had an episode in the summer of 2011 which may have represented demyelination, but we have no definite evidence to support this." Dr. Steinman explained that "definite evidence" would have been an MRI, if one had been ordered at that time. Tr. 127-28; Pet. Ex. 4 at 34. Without such testing, no "definite evidence" exists. Tr. 128-29. He added that petitioner's treating physicians made a point of noting the symptoms petitioner experienced in July of 2011. Tr. 129-30.

Dr. Steinman stated that since neither he nor the other experts in this case examined petitioner, more weight must be placed on the opinions of the treating physicians and the symptoms reported to the treating physicians by petitioner and her parents at the time. Tr. 108.

Dr. Mar stated that she placed more weight on the medical records than on petitioner's memory. Tr. 209. According to Dr. Mar, in her experience, it is quite uncommon for anyone, especially a child, to be able to remember an exact date of the first appearance of a sensory

symptom unless there is a corresponding physical trauma which occurred on a specific date. Resp. Ex. A at 5.

When questioned about petitioner's testimony regarding her inability to write and blurred vision in the fall of 2011, Dr. Mar responded that she could rely only on what was contained in the record, and in her opinion there was nothing in the record to support onset prior to January of 2012. Tr. 224-28. Dr. Mar conceded that the medical record for January 24, 2012, referenced three weeks of hand tingling, weakness in the wrists, and tripping but not falling, with a notation that "In the summer felt the same way in the leg." Tr. 256; Pet. Ex. 3 at 5. Dr. Mar agreed that facial numbness, tripping, and falling are suspicious for demyelination. Tr. 257. She conceded that the note stated that there were similar symptoms the summer before. Tr. 257.

Dr. Mar concluded that petitioner's symptoms began in January of 2012 with numbness of the left face and right hand, which resolved, followed by transient slurred speech, vertigo, and vomiting. Dr. Mar stated that petitioner was ultimately diagnosed with relapsing-remitting MS based on the attack in January of 2012 and new lesions on the MRI in February of 2012. Dr. Mar maintained her position that more weight should be placed on the medical records than on the testimony from petitioner, petitioner's mother, and petitioner's father. However, after much prodding on cross examination, Dr. Mar conceded that if she were to accept petitioner's testimony that the symptoms she suffered in July of 2011 were the same as those in the winter of 2012, with the later symptoms being more intense, she would agree that the July 2011 event was the first episode of MS. Tr. 248-51. However, in Dr. Mar's opinion, the chiropractic records in July of 2011 better supported peripheral nervous system complaints. Tr. 246-47. Dr. Mar maintained that petitioner's MS developed six months after vaccination. Resp. Ex. A at 10-11.

Having listened to testimony from petitioner, her mother, and her father, all of whom were sequestered during the others' testimony, and having heard the testimony of Dr. Steinman and Dr. Mar on the criteria for diagnosing MS, I conclude that petitioner's onset of symptoms began in July of 2011 with the numbness of her foot that ascended up her leg and into her thigh. The onset was therefore between 42 and 47 days after her June 8, 2011 Menactra vaccination.

IV. Causation Analysis and Conclusions of Law

A. Petitioner Has Met Her Burden of Showing by Preponderant Evidence that the Meningococcal Vaccine Caused or Triggered Her MS.

Under the Vaccine Act, petitioner may prevail on her claim by proving a "Table" injury, in which causation is presumed, or alternatively, by proving an "off-Table" injury, in which she identifies a causal link between the vaccine and the injury alleged. Because multiple sclerosis is not listed as a Table injury, petitioner must produce preponderant evidence that the Menactra vaccine is responsible for her injuries.

An "off-Table" claim requires that petitioner establish by preponderant evidence that a covered vaccine caused or significantly aggravated the injury claimed. § 11(c)(1)(C)(ii)(II). Petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of her condition; showing that the vaccination was a "substantial factor" and a "but for" cause of

her injury is sufficient for recovery. *Shyface v. Sec'y of Health and Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999); *see also Pafford v. Sec'y of Health and Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006) (petitioner must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of the vaccination).

Although a petitioner cannot be required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect," when petitioner files medical literature, a special master may weigh and evaluate that medical literature. *Capizzano v. Sec'y of Health and Human Servs*., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health and Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of the petitioner. *Althen v. Sec'y of Health and Human Servs.*, 418 F.3d 1274, 1280 (Fed. Cir. 2005).

The Federal Circuit has set forth three factors petitioner must satisfy to prove causation in off-Table cases. *Althen* requires that petitioners provide: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1274, 1278. All three *Althen* factors must be satisfied to prevail on an off-Table claim.

The medical theory must be a reputable one, although it need only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49. The Supreme Court's opinion in *Daubert v. Merrill Dow Pharmaceuticals, Inc.*, similarly requires that courts determine expert opinions to be reliable before they may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Daubert*, 509 U.S. 579, 590 (1993) (citation omitted). The Federal Circuit has stated that a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health and Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010).

1. *Althen* Prong One: Can the Meningococcal Vaccine Cause MS?

Dr. Steinman is an authority on MS and has spent a substantial portion of his career researching and treating this disease. Tr. 81, 83, 86. He proposed a theory in this case based upon molecular mimicry to explain the mechanism of the onset of the demyelination process in the central nervous system that becomes MS. Tr. 148. Dr. Steinman admits that there is no known cause of MS, but testified that molecular mimicry provides a sound theory through chemistry and scientific literature for the way in which some vaccines can trigger MS. Tr. 147-48.

A brief explanation of how the immune system functions, what MS is, and the components of the Menactra vaccine assists in the understanding of the theory in this case.

i. Immune System Overview

In general, a body's responses to foreign invaders, antigens[9] or pathogens, are controlled by the immune system.[10] The immune system is divided into two branches: the innate immune system and the adaptive immune system.

The innate immune system is relatively primitive and is the first line of defense when a foreign invader is encountered. Components of the innate immune system include macrophages,[11] cytokines,[12] and natural killer cells.[13]

The adaptive immune system is more advanced; it recognizes specific antigens. The adaptive immune systems contains B cells and T cells.[14] B cells make antibodies. Antibodies can be classified as different types of immunoglobulins.[15] Antibodies recognize polysaccharides (or sugars). An antibody's ability to respond to polysaccharides is one trait that distinguishes it from T cells. T cells derive their name from the thymus, where they mature.[16] T cells are divided into two groups, cytotoxic T cells and helper T cells. Cytotoxic T cells kill cells that are infected by viruses. There are many types of helper T cells: Th1 cells help cytotoxic T cells kill cells infected with infectious agents, while Th2 cells help B cells make antibodies. Th17 cells help cells at the mucosal level respond to infections by generating interleukin ("IL") 17. Interleukins are types of

[9] An antigen is any substance capable of inducing a specific immune response and of reacting with the products of that response, i.e., a specific antibody. Antigens may be toxins, proteins, bacteria, or tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant combines with an antibody. *Dorland's* at 103.

[10] "Immune system," *Dorland's* at 1861.

[11] Macrophages are cells which kill ingested microorganisms; they also digest and present antigens to T and B cells. *Dorland's* at 1093.

[12] Cytokines are proteins released by cells upon contact with an antigen, as in the generation of an immune response. *Dorland's* at 466.

[13] Natural killer cells are a type of white blood cell that contains enzymes that can kill tumor cells or cells infected with a virus. NCI Dictionary of Cancer Terms, National Cancer Institute, cancer.gov (last visited: August 31, 2017). NK cells "secrete cytokines…that stimulate and guide the response of other agents of innate immunity and lymphocytes of the adaptive immune system." *Natural Killer cells and Innate Immunity*, Ciml Immunology, Centre d'Immunologie, de Marseille-Luminy, ciml.univ-mrs.fr (last visited: August 31, 2017).

[14] *See Dorland's* at 1084, defining "lymphocytes."

[15] An antibody is an immunoglobulin molecule that interacts only with a specific corresponding antigen. *Dorland's* at 100. Immunoglobulins are glycoproteins which function as antibodies. *Id*. at 919.

[16] The thymus is an organ that produces T cells. *Dorland's* at 1925.

cytokines.[17] Cytokines are proteins by which cells of the immune system communicate; they either stimulate or inhibit proliferation, differentiation, and function of cells of the immune system. Another type of helper T cell, the T regulatory cells, ensures that the immune system does not over respond.

ii. MS and the central nervous system

MS is a chronic inflammatory disease of the myelin of the central nervous system. Part of a nerve cell, or neuron, is the axon, which conducts electrical impulses through the brain and the spinal cord. The axon is covered in myelin.[18] In MS, "the inflammatory process is characterized by focal infiltration of T cells, B cells and macrophages, and by loss of myelin."[19] This means that immune cells have entered the central nervous system and caused inflammation, resulting in the deterioration of the myelin sheath that covers the axon. MS is classified as a "demyelinating" disease due to the disruption it causes to the myelin.[20]

According to Dr. Steinman, clinical experience shows that the immune system is active outside of the central nervous system, which consists of the brain and spinal cord. Tr. 101. The migration of activated T cells, B cells, or macrophages into the central nervous system will penetrate the blood brain barrier. Tr. 143. Dr. Steinman explained that Tysabri, the most approved drug for MS, works by blocking the movement of immune cells (the T cells, B cells, and macrophages) and inflammation from getting to the brain. [21] Tr. 101.

[17] "Interleukin" is a generic term for a group of cytokines produced by immune cells. *Dorland's* at 949.

[18] The myelin sheath is the cylindrical covering on the axons of some neurons. It is interrupted at intervals along its length by gaps known as nodes of Ranvier. Myelin is an electrical insulator that serves to speed the conduction of nerve impulses. *Dorland's* at 1701-02.

[19] Kal W. Wucherpfennig et al., *Recognition of the Immunodominant Myelin Basic Protein Peptide by Autoantibodies and HLA-DR2-restricted T Cell Clones from Multiple Sclerosis Patients*, J. CLIN. INVEST., 100(5): 1114-22 (1997), filed as Pet. Ex. 23, at 1114.

[20] Other central nervous system demyelinating diseases include transverse myelitis, optic neuritis, and ADEM. MS differs from these diseases because the latter are generally considered monophasic, occurring by only one phase or stage.

[21] Dr. Steinman noted that he is well versed on Tysabri and how it works because it was developed in his lab and he has written many articles about it. In an article entitled *Autoimmune Disease: Misguided assaults on the self-produced multiple sclerosis*, written for SCIENTIFIC AMERICAN, he described the Velcro-like molecule called alpha 4 integrin and an antibody connected to alpha 4 integrin which can block the lymphocytes into the brain in detail with how Tysabri works. Tr. 143-44; Pet. Ex. 34.

Dr. Mar agreed that medications for MS work by suppressing the T cells, B cells, and lymphocytes, and preventing them from migrating across the blood brain barrier. Tr. 197. They both agreed that there is no known cause of MS. Tr. 145, 251.

iii. Structure of the Menactra vaccine

Dr. Steinman testified to the components of the Menactra vaccine. He began by noting that the surface of the meningococcal bacterium is covered with polysaccharides which are a chain of sugar molecules called "mannose." Tr. 89-90; Resp. Ex. A-6 at 5; *see also Dorland's* at 1493. The vaccine itself contains four polysaccharides from the coat of the meningococcus bacterium, meningococcal A, C, Y, and W-135. Tr. 87, 89; Pet. Ex. 44 at 4. Polysaccharides are used in the vaccine to invoke an immune response to the meningococcus bacteria. Tr. 89. ("Glycan" is a generic term describing molecules with glycoside bonds; this includes sugars. The experts frequently interchanged the words "glycan," "polysaccharides," and "sugars" in referring to the polysaccharides in Menactra during the hearing. Resp. Ex. A at 7.) Dr. Halsey noted that each of the polysaccharides is different, which is why all four polysaccharides had to be included in the Menactra vaccine. Tr. 301.

According to Dr. Steinman, since the polysaccharides alone would not evoke a strong enough response from the immune system to recognize and kill meningococcal bacteria, each individual polysaccharide is conjugated (coupled) to a protein to increase the immune response. In Menactra, that protein is diphtheria toxoid. Tr. 87-89, 91- 92; Pet. Ex. 17 at 7. Diphtheria toxoid is the toxin produced by diphtheria bacteria, chemically treated so that it is harmless, but still able to elicit an immune response. Tr. 91. Dr. Mar agreed with Dr. Steinman that the meningococcal polysaccharides are conjugated to diphtheria toxin within the Menactra vaccine to produce a greater immunogenic effect. Tr. 241-42.

Dr. Steinman explained that if a person who has received the Menactra vaccine is exposed to the meningococcal bacteria, his or her body will recognize the polysaccharide coat on the outside of the bacterium, and will rapidly eradicate the infection. Tr. 89-90.

Dr. Halsey also provided in depth testimony about the components of Menactra vaccine and the conjugation of the polysaccharides to CRIM protein to secure improved antibody response. Tr. 276-78. He explained that CRIM protein was approved by the FDA and administered to "tens of millions" of children, and that the polysaccharides in Menactra, meningococcal A, C, W, and Y, do not cross react with human tissue. Tr. 278-81.

However, Dr. Halsey later clarified that he was mistakenly describing the new meningococcal B products, not the Menactra vaccine.[22] Tr. 316. Dr. Halsey explained that the new meningococcal B vaccine was made without polysaccharides because the meningococcal B cross-reacted with human brain tissue. Tr. 279-81. The new vaccine is being manufactured with a totally different method, using only components of the outer wall of the bacterium to make the vaccine. Tr. 281. Dr. Halsey conceded that petitioner did not receive the meningococcal B vaccine.

[22] Dr. Halsey is involved in the development of the new meningococcal B vaccine.

Having laid a foundation for how the immune system works, what MS is, and the structure of the Menactra vaccine, I turn to Dr. Steinman's theory in this case.

iv. Petitioner's immune system initiated a two pronged response to the meningococcal vaccine which triggered multiple sclerosis

Dr. Steinman submitted that molecular mimicry is an accepted, "standard, well-supported theory based on chemistry." Tr. 114-15. A "mimic" is a chemical structure that, either because of its primary sequence or its shape, resembles something else. Tr. 115. A chemical structure can trigger an immune response, but if a sugar on a bacterium has a similar chemical structure to a sugar in the nervous system, "there could be trouble." Tr. 115.

Dr. Steinman submitted that in this case, the innate immune system activated an immune response to the polysaccharides in the Menactra vaccine; then the adaptive immune system called up the memory cells that recognized the diphtheria toxoid in the vaccine from prior exposure to DTaP/DT vaccines and caused a two-pronged response. Pet. Ex. 17 at 16, 17 (citing to Pet. Ex. 29-32); Tr. 105-06, 109-10, 121-22.[23]

Dr. Steinman explained that there are similarities between the glycans in the Menactra vaccine and certain structures in the central nervous system, in particular contactin, which is a component of myelin. Contactin is located at the node of Ranvier, where the electricity in an axon jumps from one node to another. Tr. 110, 112, 122. The contactin was modified by the sugars/glycans in the meningococcus. Tr. 112. When the antibody attacks the glycan on the contactin it damages the axon, interrupting the electricity being conducted in the central nervous system and leads to MS. Tr. 122; Pet. Ex. 17 at 16; Pet. Ex. 30, 31, 32.

Dr. Steinman stated that the immune system had an aberrant reaction to both the diphtheria toxoid protein and the polysaccharide coat of the Menactra vaccine, damaging the central nervous system and triggering MS in the process. Tr. 112, 122.

Part One of Dr. Steinman's theory: The glycans in the meningococcal vaccine resemble glycans in the brain

In support of his theory that molecular mimicry could be responsible for the Menactra vaccine damaging the central nervous system and triggering MS in this case, Dr. Steinman presented some of his own research as well as studies and research done by others. *See generally* Pet. Ex. 23, 25, 26, 28.

[23] Dr. Steinman's theory relies on the person having an immunity to diphtheria toxoid from previously receiving DTaP or DT vaccinations.

Dr. Steinman presented the Wang study which showed the presence of anti-glycan antibodies in the cerebrospinal fluid in MS. In the Wang study (Pet. Ex. 22[24]), experimental autoimmune encephalomyelitis ("EAE") was produced in animals when myelin products with shared pathogens to vaccines and host myelin antigens were introduced. The antigens from the pathogens, or vaccines, activated myelin reactive lymphocytes which then migrated into the central nervous system and attacked the myelin. Many myelin peptides have a similarity to viral sequences and can cause cross-reactive T cell responses. In this study, encephalitis was provoked by a vaccination with spinal cord homogeny in complete Freund's adjuvant followed by pertussis toxin, which showed that EAE was similar to acute hemorrhagic leukoencephalitis when the animals were exposed to intravenous meningococcal toxin. According to Dr. Steinman, the study found glycan antibodies to mannose clusters in both MS lesions and spinal fluid of patients with MS. Tr. 120-21; Pet. Ex. 17 at 7-10; Pet. Ex. 22 (finding anti-glycan antibodies in the cerebrospinal fluid of patients with MS. *Id.* at 1, 14).

Dr. Mar did not dispute that molecular mimicry was a valid scientific theory, but she did not agree that it applied in this case. "[O]ne cannot merely present the theory of molecular mimicry and based upon the general acceptance of the molecular mimicry theory, jump to the conclusion that it is meningococcal vaccine that provokes certain individuals to an autoimmune response causing MS." Resp. Ex. A at 8.

Dr. Mar agreed that MS is immune-mediated and that autoantibodies, T cells, and molecular mimicry all play a role in the pathology of MS; however, this is only a theory and has been tested only in animal EAE models. Tr. 234-35. She disagreed with Dr. Steinman's reliance on the Wang study, however, stating that glycans are poorly immunogenic. Therefore, finding glycan antibodies to mannose clusters in MS lesions does not mean that we know what the specific mannose cluster antigens of these MS patients are. Tr. 241; Resp. Ex. A at 7. Dr. Mar stated that the antigen preparation in the Wang study was Ribonuclease B with Man5-6 GLCNAc2, which is different than the chemical structure of meningococcal A. Resp. Ex. A at 7. According to Dr. Mar there was no evidence that patients with MS in this study had antibodies specific to meningococcal A glycan. *Id*. She also pointed out that the Wang study showed that the anti-glycan antibody response was associated with a significantly reduced clinical severity of EAE; therefore, anti-glycan antibodies may be helpful antibodies rather than a cause of demyelination. *Id.*

Dr. Mar countered with an article by Wraith,[25] which stated "molecular mimicry in itself is not sufficient to trigger autoimmune pathology, and other factors intrinsic to infections, such as tissue damage and long lasting inflammatory reaction, might be required as well." Resp. Ex. A at 7-8; Resp. Ex. A-8. Dr. Mar agreed that while "there is clear genetic predisposition for some autoimmune disease…environmental factors also play a crucial role." *Id*.

---

[24] Denong Wang et al., *Unconvering Cryptic Glycan Markers in Multiple Sclerosis (MS) and Experimental Autoimmune Encephalomyelitis (EAE)*, DRUG DEV RES., 75: 172-88 (2014), filed as Pet. Ex. 22.

[25] David C. Wraith, et al., *Vaccination and autoimmune disease: what is the evidence?*, LANCET, 362: 1659-66 (2003), filed as Resp. Ex. A-8.

According to Dr. Halsey, all of Dr. Steinman's references to articles on molecular mimicry are irrelevant to the pathogenesis of MS. Resp. Ex. C at 8, citing Pet. Ex. 17, 24, 25, 27.[26] The Wang study[27] did not study meningococcal polysaccharides; it studied the mannose and glycans in an artificial system, an EAE mouse model. Tr. 300; Pet. Ex. 22. Dr. Halsey added that the sugars in the study were administered with Freund's complete adjuvant. Freund's adjuvant contains mineral oil, water, and microbacteria, all very inflammatory products. Tr. 301; Pet. Ex. 22. According to Dr. Halsey, even if the authors had used meningococcal polysaccharides, administering them with an inflammatory substance like Freund's adjuvant in an effort to induce central nervous system inflammation would not provide evidence that the polysaccharides were causing the inflammation. Tr. 301. Further, Dr. Halsey noted that, though the authors indicated that they had found potential markers that may be used for diagnostic or therapeutic purposes, they did not state or imply that they had found evidence that specific infections or vaccines can cause MS. Resp. Ex. C at 6-7; Pet. Ex. 22 at 4-5.

Dr. Steinman conceded that the Wang study did not demonstrate that the glycan antibodies caused or worsened the disease in mice; in fact, the study showed that the mice got better. Tr. 157. However, he stated that if he were to inject a mouse with the meningococcal vaccine and the mouse got worse, it would not show that Menactra caused MS; rather, it would be evidence that he could mimic something that looked like MS in a mouse and that the glycans affected the EAE model. Tr. 170.

Dr. Halsey further opposed Dr. Steinman's theory by referencing the Jack article (Pet. Ex. 46[28]), which found that a deficiency in mannose binding lectin ("MBL") was associated with an increased risk of meningococcal, pneumococcal, and other infections. Tr. 301. MBL is part of the innate immune system and fights off infection. Tr. 301. This deficiency explains how such an invasive disease as meningitis is so rare. Tr. 302-03. According to Dr. Halsey, Dr. Steinman's theory discusses the adaptive immune system, though Dr. Halsey agrees that Dr. Steinman seems to combine the innate and adaptive systems. However, Dr. Halsey states that since the MBL that would attack the polysaccharides on the surface of the bacteria in the Menactra vaccine is in the innate immune system, there would be no cross reactivity between human brain tissue and the four polysaccharides. Tr. 302-05.

According to Dr. Halsey, there are two ways to assess causality between a vaccine and an event. One is to look for evidence of increased risk in people who receive a vaccine compared to people who did not. The second is to look at a specific laboratory study that could implicate a

---

[26] Pet. Ex. 17 (Dr. Steinman's expert report), Lawrence Steinman, *Autoimmune Disease*, SCIENTIFIC AMERICAN, 107-14 (1993), filed as Pet. Ex. 24; Lawrence Steinman and Michael B.A. Oldstone, *More mayhem from molecular mimics*, NATURE MEDICINE, 3(12): 1321-22 (1997), filed as Pet. Ex. 25; Jean-Francois Bach, *The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases*, N ENGL J MED, 347(12): 911-20 (2002), filed as Pet. Ex. 27.

[27] Wang et al. *supra* at note 24, Pet. Ex. 22.

[28] Dominic L. Jack et al., *Mannose-binding lectin enhances phagocytosis and killing of* Neisseria meningitidis *by human macrophages*, J. LEUKOC. BIOL., 77: 328-36 (2005), filed as Pet. Ex. 46.

component of the vaccine, whether antigen or adjuvant, to an adverse event. Tr. 296-97. When asked wasn't that what Dr. Steinman had done here, Dr. Halsey's response was "no," Dr. Steinman did not study any component of the vaccine that would demonstrate any evidence of a causal relationship with MS in petitioner or any other patient with MS. Tr. 297.

Neither Dr. Mar nor Dr. Halsey disputed that molecular mimicry was a valid scientific theory. In fact, Dr. Mar clarified that she was not suggesting that molecular mimicry had no role in petitioner's development of MS. Resp. Ex. A at 8. Neither Dr. Mar nor Dr. Halsey disputed the fact that in the studies relied upon by Dr. Steinman, glycan antibodies to mannose clusters in both MS lesions and spinal fluid of patients with MS were found. Tr. 120-21; Pet. Ex. 17 at 7-10; Pet. Ex. 22 (finding anti-glycan antibodies in the cerebrospinal fluid of patients with MS. *Id.* at 1, 14).

Part Two of Dr. Steinman's Theory: Diphtheria toxoid in the meningococcal vaccine stimulated the adaptive immune system to produce B memory cells

For this part of his theory, Dr. Steinman cited to the Salmi study (Pet. Ex. 21[29]) to demonstrate how antibodies created in response to diphtheria toxoid vaccine can enter the brain through intrathecal synthesis.[30] Tr. 118. In Salmi, 30 MS patients and 30 neurological control patients were measured for antibodies to diphtheria and tetanus toxoids by enzyme-immunoassays. The frequency of antibody-positive patients and the titer distribution was similar in both groups. In spite of this, some of the MS patients had intrathecal antibody synthesis to these toxoids. None of the individuals had diseases caused by diphtheria or tetanus bacteria but they all had been vaccinated 2 to 24 years before the clinical symptoms of MS. Pet. Ex. 21 at 1.

According to Dr. Steinman, the Salmi study showed oligoclonal bands related to diphtheria toxoid found in the central nervous system of children who had not been vaccinated for diphtheria in years. Tr. 119. Oligoclonal bands are proteins called immunoglobulins. Pet. Ex. 17 at 6-7. The presence of these proteins in the CSF indicates inflammation in the central nervous system and is a sign of multiple sclerosis. Pet. Ex. 17 at 7. Dr. Steinman proposed that these findings supported his theory that the antibodies from diphtheria and tetanus toxoid exposure had nested in the brain and resulted in lasting memory within the brain. Tr. 119; Pet. Ex. 21 at 6-7. Therefore, when the Menactra vaccine was given in this case, petitioner's adaptive immunity activated an antibody response to the glycans and diphtheria toxoid, both triggering various pathogenic pathways known to be involved in MS. Pet. Ex. 17 at 6.

Dr. Mar criticized Dr. Steinman's reliance on the Salmi study, pointing out that the study was performed 33 years ago, was extremely small, and the data was based on one patient with "positive" results. Tr. 217-18, Resp. Ex. A at 7. Dr. Mar submitted the Massa study in contrast

[29] A. Salmi et al., *Intrathecal synthesis of antibodies to diphtheria and tetanus toxoids in multiple sclerosis patients*, J NEUROIMMUNOL., 1(3): 333-41 (1981), filed as Pet. Ex. 21, Resp. Ex. C-16.

[30] "Intrathecal synthesis" means that the antibodies to diphtheria and tetanus toxoid were made within the cerebrospinal fluid ("CSF"). Pet. Ex. 17 at 6-7.

(Resp. Ex. A-4[31]), which looked at serum titers of antibodies against tetanus and diphtheria toxoids and found that neither diphtheria nor tetanus toxoids are risk factors for MS. Resp. Ex. A at 7. Dr. Mar concluded that there was no study to date that had proven that diphtheria toxoid can cause demyelinating disease in MS. Tr. 219; Resp. Ex. A at 7.

However, Dr. Mar did agree that diphtheria antibodies can be found in patients with MS. Her explanation for this was that in patients with MS, the myelin and axons are damaged, the blood brain barrier becomes "leaky," and the immunology is "messed up." Tr. 219. As a result, it is not surprising that these antibodies are found; the antibodies have been studied, and they are not pathogenic, but rather secondary to MS. Tr. 219; 223-24.

Dr. Halsey testified that in Salmi, the antibodies studied in a small number of patients with MS were targeted against antigens which were not derived from meningococcal organisms or vaccines. Tr. 298. According to Dr. Halsey, though the hypothesis was that these antigens may play a role in the pathogenesis of MS, it was also very likely that these findings had no relevance to a causal association, but were only markers for the disease. Resp. Ex. C at 8. Dr. Halsey stated that Dr. Steinman highlighted only the patient who had evidence of intrathecal production of diphtheria toxoid. There were also patients with intrathecal production of tetanus and measles. Tr. 298. Dr. Halsey stated that since antibody producing cells enter the central nervous system from the bloodstream, talking about one or two patients with evidence of intrathecal production of diphtheria does not provide evidence of causal relationship. Tr. 298-99. Dr. Halsey pointed out that the conclusion in Salmi was "It is not known whether the intrathecal immunoglobulin production has any etiological or pathogenic importance in MS." Resp. Ex. C at 5; Pet. Ex. 21 at 2. In addition, "…At an unknown time between the vaccinations and sampling these committed cells had entered the brain of these patients. It has not been shown that antibodies to diphtheria or tetanus toxoids have any specific affinity to brain tissues." Resp. Ex. C at 5; Pet. Ex. 21 at 7.

According to Dr. Halsey, over 20 different microorganisms have been found and thought to be a potential cause of MS, sometimes based on intrathecal production; diphtheria just happened to be one of the diseases that was found. Tr. 299. Focusing on one or possibly two patients with evidence of intrathecal production of diphtheria does not provide evidence of a causal connection to MS. Tr. 299.

The role of epidemiology

Acknowledging that there were no epidemiological studies linking Menactra to MS, Dr. Steinman analogized Guillain-Barré Syndrome ("GBS") following influenza vaccine to bolster his theories in this case. Tr. 92-93. GBS is a serious neurological disorder involving inflammatory demyelination of peripheral nerves characterized by progressive, symmetrical weakness in the legs and arms, with loss of reflexes.[32] GBS can be caused by infections.

---

[31] J. Massa et al., *Serum titers of IgG antibodies against tetanus and diphtheria toxoids and risk of multiple sclerosis*, J NEUROIMMUNOL., 208 (1-2): 141-42 (2009), filed as Resp. Ex. A-4.

[32] GBS is a rapidly progressive ascending motor neuron paralysis which begins with paresthesia of the feet, followed by paralysis of the entire lower limbs ascending to the trunk, upper limbs, and face. *Dorland's* at 1832.

According to Dr. Steinman, GBS looks like MS but occurs outside of the central nervous system. Tr. 139. Dr. Steinman submitted that the best example of molecular mimicry in a neurological disease involves GBS after a campylobacter infection, where the mimic is a sugar called "ganglioside." Tr. 114, 116, 139. Dr. Steinman pointed out that Wraith did not discount molecular mimicry but rather discussed the requirement for epidemiology to prove that a vaccine causes a disease by molecular mimicry, Tr. 136; Resp. Ex A-8. Dr. Steinman explained that epidemiologic studies are complex and expensive; therefore, they are not always available. Tr. 137. However, a lack of epidemiological support does not mean the theory is inaccurate. Tr. 137.

Dr. Steinman submitted articles by Schonberger[33] (finding an increase in cases of GBS following widespread administration of the influenza vaccine) and Langmuir[34] (finding an increase in cases of GBS reported in association with the administration of the 1976 swine flu vaccine) in support of his theory, acknowledging that they were the best surrogates he could find. He also noted that the Institute of Medicine has said that there is insufficient epidemiology to rule out Menactra as a potential cause or trigger of MS. Tr. 104; 138; 173.

Dr. Steinman stated that the Schonberger and Langmuir articles supported onset of demyelinating disease from around seven to eight weeks; Dr. Langmuir actually extended the onset period to 60 days. Tr. 139-40. According to Dr. Steinman, in this case, MS involves the CNS and the migration of an activated T or B cell into the CNS. An activated T cell, B cell, or macrophage could pass through the blood brain barrier and, with the immune system's memory of the diphtheria toxoid, the timing of onset would be the same as with peripheral demyelination, such as GBS. Tr. 141-42.

According to Dr. Halsey, who was peripherally involved with the Schonberger study, Dr. Schonberger demonstrated an increased risk of GBS following receipt of the influenza vaccine. Tr. 294-95. Dr. Langmuir, a former CDC official, reached the same conclusion as the Schonberger study. Tr. 295. According to Dr. Halsey these studies have no relevance in this matter or to MS, because MS is a "very different" disease than GBS. Tr. 295.

Dr. Mar stated that there was no peer reviewed study discussing molecular mimicry between meningococcal polysaccharide A and MS or diphtheria toxoid and MS. Resp. Ex. A at 7. Additionally, there were no peer reviewed publications within respected medical or scientific journals in which a study has concluded the existence of a temporal relationship between meningococcal vaccination events and the onset of MS. *Id*. at 4. Furthermore, scientifically and epidemiologically sound studies have been published concluding that there is no causal mechanistic association between vaccines and any CNS acute demyelinating disease, including MS. *Id*. at 8-9. Though it is generally understood that auto antibodies, T cells, and molecular

---

[33] Lawrence B. Schonberger et al., *Guillain-Barre Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-77*, AM J EPIDEMIOL, 110(2): 105-23 (1979), filed as Pet. Ex. 33, Resp. Ex. C-18.

[34] Alexander D. Langmuir et al., *An Epidemiologic and Clinical Evaluation of Guillain-Barre Syndrome Reported in Association with the Administration of Swine Influenza Vaccines*, AM J EPIDEMIOL, 119(6): 841-79 (1984), filed as Pet. Ex. 34.

mimicry may contribute to the symptoms and pathology of MS, there is no scientific evidence linking the mechanisms in MS to meningococcal vaccine. *Id*. at 10. Accordingly, a causal connection between meningococcal vaccination and MS is lacking. *Id*. at 4.

Dr. Mar was questioned about the Velentgas study (Resp. Ex. A-16[35]), which was conducted after five cases of GBS were reported following the introduction of the meningococcal vaccine in 2005. Resp. Ex. A-16 at 1. Dr. Mar stated that there is a need for epidemiology for a causal relationship, but there was no epidemiology done here, and therefore the study should not be relied on. Tr. 243; Resp. Ex. A-16. Dr. Halsey agreed. Tr. 292.

Dr. Mar conceded that the IOM has recognized GBS following vaccinations, but added that GBS is a peripheral, not central nervous system, demyelinating disease. Tr. 229-30.

Dr. Halsey stated that epidemiology is necessary, and in addition to immunologic studies, it is the primary method used to investigate "rare adverse events." Tr. 281-82; Pet. Ex. 44 at 7. There are no epidemiologic studies implicating meningococcal infections or vaccines as risk factors for development of multiple sclerosis. Resp. Ex. C at 4. He further stated that epidemiologic studies are the only way to answer questions of risk intervals following vaccines. *Id.* at 8, citing Resp. Ex. C-15.[36]

According to Dr. Halsey, Dr. Steinman's references to articles dealing with GBS for epidemiological support are incorrect because GBS differs from MS in clinical presentation, risk factors, areas of the central nervous system affected, and pathologic mechanisms. *Id*., citing Resp. Ex. C-13.[37] "It is inappropriate to extrapolate conclusions from GBS and apply them to MS." Resp. Ex. C at 8; Resp. Ex. C-18;[38] Resp. Ex. C-19.[39]

Dr. Halsey also dismissed petitioner's references to the FDA and CDC investigation of five reports of GBS following the meningococcal vaccine, stating that there was no increased risk found. Tr. 289; *see also* Pet. Ex. 52, 53, and 54.[40] However, he admitted that the GBS studies may

---

[35] Priscilla Velentgas et al., *Risk of Guillain-Barre syndrome after meningococcal conjugate vaccination,* PHARMACOEPIDEMIOL DRUG SAF., 21: 1350-58 (2012), filed as Resp. Ex. A-16.

[36] Ali Rowhani-Rahbar, et al., *Biologically plausible and evidence-based risk intervals in immunization safety research*, VACCINE, 31: 271-77 (2012).

[37] Joaquin A. Pena and Timothy E. Lotze, *Pediatric Multiple Sclerosis: Current Concepts and Consensus Definitions,* AUTOIMMUNE DISEASES, 2013: 1-12.

[38] Lawrence B. Schonberger et al., see n. 33 *supra,* filed as Pet. Ex. 33, Resp. Ex. C-18.

[39] James J. Sevjar, *Vaccines and Neurologic Disease*, SEMIN NEUROL, 31: 338-55 (2011).

[40] "FDA/CDC Alert on New Meningococcal Vaccine," Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, originally posted Oct. 7, 2005, last updated June 9, 2016, http://vaccinesafety.edu/Menactra-GBS.htm, filed as Pet. Ex. 52; "Meningococcal Vaccine," Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, last

not have been available to the IOM when they concluded that there is insufficient evidence to accept or reject whether Menactra could cause MS. Tr. 316-17. Additionally, Dr. Halsey noted that there were at least four other alerts which provoked further monitoring and surveillance and larger epidemiological studies over a two year period. Tr. 291.

Dr. Halsey testified that the CDC and the FDA have surveillance systems that report adverse reactions. Tr. 282. According to Dr. Halsey, the Clinical Immunization Assessment Network works with scientists from the CDC and FDA as well as public health officials to look for reactions after vaccines. Tr. 282, 320. Dr. Halsey himself is involved in this process. Tr. 283. Individual case reports are discussed on a weekly basis to determine whether the adverse reaction occurred by chance or whether there is evidence of a biological mechanism. Tr. 283. Statistics are viewed and individual case reviews are conducted to further review and develop protocols and collect adverse health outcomes. Tr. 283-84. According to Dr. Halsey, there has been no signal of an increased rate of MS following Menactra vaccine. Tr. 284. Dr. Halsey admitted that he was unaware if VAERS is a mandatory or voluntary reporting system.[41] Tr. 318-20.

Dr. Halsey explained that adverse reactions are viewed in the context of the natural incidence of the disease at the age of the vaccine recipients, the other vaccines being administered to the same age group, and the rate at which other vaccines are administered. Tr. 285. Dr. Halsey clarified that there have been reports of MS after vaccination, but the number of reports has not risen to the level that would necessitate investigation. Tr. 285-86, 311. When asked how many reports were necessary to trigger an investigation, Dr. Halsey stated that it would depend on the age of the population, other vaccines being administered to the same age group, and the rates of the same reaction occurring after other vaccines. Tr. 286. Essentially, Dr. Halsey could not provide a definitive answer as to how many incidents would need to be reported before an investigation into the safety of the vaccine would take place.

Dr. Halsey disagreed that the meningococcal vaccine had anything to do with petitioner's development of MS. Tr. 276. However, he admitted that he specializes in infectious disease, is not a neurologist, is not a specialist in MS, and has never made a diagnosis of MS. Tr. 310, 320. Dr. Halsey further admitted that MS is not an infectious disease; it is an autoimmune disease. Tr. 310, 322. Dr. Halsey admitted that there is still uncertainty of the connection between certain viruses and MS. Tr. 321-22.

---

updated June 9, 2016, http://www.vaccinesafety.edu/cc-mening.htm, filed as Pet. Ex. 53; "Guillain-Barre Syndrome Among Recipients of Menactra Meningococcal Conjugate Vaccine – United States, June –July 2005," CDC Morbidity and Mortality Weekly Report, 54(Dispatch); 1-3 (2005), http://www.cdc.gov/mmwr/preview/mmwrhtml/mm54d1006a1.htm, filed as Pet. Ex. 54.

[41] "VAERS" is the Vaccine Adverse Event Reporting System. It "accepts and analyzes reports of adverse events (possible side effects) after a person has received a vaccination….VAERS is a passive reporting system, meaning it relies on individuals to send in reports of their experiences…." While anyone can report an adverse event, healthcare professionals are required to report certain adverse events, and vaccine manufacturers are required to report all adverse events that come to their attention. "About VAERS," VAERS Vaccine Adverse Event Reporting System, vaers.hhs.gov/about.html (last visited: August 31, 2017).

The Federal Circuit has held that petitioner's burden is to show that it is more likely than not that a disease was caused by a vaccine "in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280.

Both Dr. Mar and Dr. Halsey agreed that environmental factors and genetic predisposition are factors in MS and that the cause of MS is elusive. Respondent's experts' most adamant argument was that there is no epidemiological studies to prove that Menactra causes MS. However, the presence of epidemiological studies is not the standard.

I find, based on literature, testimony, and affidavits, that Dr. Steinman presented a biologically plausible theory to explain how the Menactra vaccine can act as a trigger of MS through molecular mimicry and antigen memory. Therefore, petitioner has established the first prong of *Althen* by a preponderance of the evidence.

2. *Althen* Prong Two: Did the Meningococcal Vaccine Cause or Trigger Petitioner's Development of MS?

The theory proposed in *Althen* prong one and the logical explanation for prong two in this case are closely tied together. Dr. Steinman described the components of the Menactra vaccine and how the combination of polysaccharides and prior exposure to diphtheria toxoid used as the activating agent in Menactra could disrupt the myelin in the brain of a vulnerable individual by activating the immune system during which an error occurs and the T-cells, B cells, and macrophages responding attack the central nervous system. That is the concept of molecular mimicry. The accepted theory of MS is the formation of a group of autoreactive T cells that become activated outside of the central nervous system and travel into the central nervous system. If they encounter a myelin antigen and there is an aberrant response, MS will develop. Dr. Steinman's theory supports that response in this case.

In addition to *Althen* being the standard in these cases, the Federal Circuit affirmed the decision in *Althen* which involved a tetanus toxoid vaccine causing demyelinating disease in the form of ADEM and optic neuritis. *See generally Althen*, 418 F.3d 1274. Since then, there have been several cases where special masters ruled in favor of petitioners who developed demyelinating disease after vaccination. *See Smith v. Sec'y of Health & Human Servs.*, No. 08-864V, 2016 WL 2772194 (Fed. Cl. Spec. Mstr. Apr. 18, 2016)(awarding compensation for MS linked to a hepatitis B vaccine); *Jane Doe/74 v. Sec'y of Health & Human Servs.*, No. [Redacted] (awarding compensation for TM and MS linked to tetanus-diphtheria and measles-mumps-rubella ("MMR"), hepatitis B, and meningococcal vaccines); *Johnson v. Sec'y of Health & Human Servs.*, No. 99-219V, 2000 WL 1141582 (Fed. Cl. Spec. Mstr. Jul. 27, 2000)(awarding compensation for ADEM linked to a tetanus-diphtheria ("Td") vaccine); *Hargrove v. Sec'y of Health & Human Servs.*, No. 05-694V, 2009 WL 1220986 (Fed. Cl. Spec. Mstr. Apr. 14, 2009)(awarding compensation for TM linked to a diphtheria-tetanus-acellular pertussis ("DTaP") vaccine and/or other vaccinations); *Werderitsh v. Sec'y of Health & Human Servs*., No. 99-310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006)(awarding compensation for MS linked to a hepatitis B vaccine).

The theory in all of the cases in which the petitioner prevailed is the same: the antigenic insult of the vaccine can cause the recipients to develop antibodies to their own myelin sheath, causing lesions in the brain, the spinal cord, or both, and resulting in demyelinating disease within a proper temporal period. According to the Federal Circuit, "requiring either epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect is contrary to what we said in *Althen*…" *Capizzano*, 440 F.3d at 1325. Therefore, as long as a petitioner satisfies the three *Althen* prongs, a lack of epidemiological studies will not prevent petitioner from prevailing. *See Knudsen*, 35 F.3d at 550; *Althen*, 418 F.3d at 1280.

Petitioner was a healthy, active 14 year old when she developed MS 42 to 47 days after receiving the Menactra vaccine. The meningococcal vaccine triggered an aberrant immune response in petitioner, resulting in her development of MS. Tr. 122. For this petitioner, her MS was due to a combination of her unique immune response to specific components of the Menactra vaccine, and her predisposition, by virtue of being female[42] and having a family history of her mother's subclinical lesions, which made for a predisposition for MS or autoimmunity. Tr. 175.

The undersigned accepts Dr. Steinman's theory of how the meningococcal vaccine could trigger MS in this case and I find that the theory fits the facts in this case. Petitioner received the meningococcal vaccine, the components of which, particularly the diphtheria toxoid and the meningococcal polysaccharides, triggered demyelination in the central nervous system of petitioner, who may have already been predisposed to develop MS. The onset of symptoms is consistent with MS, including petitioner's leg numbness, which began in the foot and spread into the calf and thigh in July of 2011, blurry vision, inability to write, and stuttering, which came and went until the symptoms became too pronounced to disregard in January of 2012. Petitioner was diagnosed with relapsing-remitting MS in February of 2012, having had several episodes of symptoms. Respondent suggested that petitioner's stuffy nose over a three week period was symptomatic of a viral or bacterial illness, but there was little in the record to support that petitioner was ill, and not merely suffering from allergies. No other explanation for an environmental trigger appears in the evidence, and accordingly, it is reasonable to conclude that the vaccine provided the necessary trigger for the onset of her MS.

Petitioner has established prong two.

3. *Althen* Prong Three: Timing

As set forth above at length, Dr. Steinman opined that 42 days for a person to develop autoimmune reaction is medically appropriate. Tr. 137-38. The Schonberger and Langmuir articles extended the onset of GBS up to eight weeks. Tr. 140; *see also* Pet. Ex. 33, 34. Here, petitioner has MS, a disorder of the central nervous system, and the onset of her symptoms was within 42 to 47 days, which is medically appropriate. Tr. 141.

[42] Dr. Steinman testified that women are two to four times more likely to develop MS than men. Tr. 172-73.

Neither of respondent's experts addressed or disagreed with Dr. Steinman's argument regarding the 42 to 47 days for onset of demyelinating disease following vaccination.

According to Dr. Steinman, given a petitioner who is already predisposed to developing MS due to inherited susceptibility from her mother and being female, combined with what vaccines can do, what antibodies can do, the nature of the nervous system of a person with MS and the nature of the pathology of MS, a clear manifestation of MS could occur within 42-43 days after getting the Menactra vaccine. Tr. 172-73.

Based on the medical records and the testimony of the petitioner and her family, petitioner's symptoms of MS began in July of 2011. The onset within 42 to 47 days has been accepted as a reasonable timeframe for the onset of an autoimmune response triggered by a vaccine. I have concluded that, consistent with Dr. Steinman's testimony, and as cited above, petitioner's onset of symptoms was in July of 2011, 42 to 47 days after her vaccine. This is a reasonable timeframe for the trigger of the disease onset in this case.

Petitioner has satisfied prong three.

B. Burden Shifting: Respondent Must Show an Alternative Cause of Injury

Because petitioner has established a prima facie case, she is entitled to compensation unless respondent can put forth preponderant evidence that petitioner's injury was in fact caused by factors unrelated to the vaccine. *Whitecotton v. Sec'y of HHS*, 17 F. 3d 374, 376 (Fed. Cir. 1994) *rev'd on other grounds sub nom*. *Shalala v. Whitecotton*, 514 U.S. 268 (1995); *see also Walther v. Sec'y of HHS*, 485 F. 3d 1146, 1151 (Fed. Cir. 2007).

Both Dr. Mar and Dr. Halsey agreed that certain environmental factors can increase the risk of developing MS. Tr. 190-91; Resp. Ex. C at 4. Dr. Mar also noted that most MS patients have a history of viral infection. While experts have researched previous viral infections such as Epstein-Barr virus, cytomegalovirus, and herpes simplex virus Type 1, they have not been able to determine the role of these viruses in the pathology of MS. Tr. 192; Resp. Ex. C at 4.

Dr. Mar, like Dr. Steinman, agreed that MS has "a lot" of genetic components. Tr. 190. (Dr. Steinman: There are a hundred genes associated with MS. Tr. 95.) Genetic factors are "much stronger" in children; the International Pediatric MS Study Group is currently looking at this. Tr. 190.

Petitioner described having a stuffy nose for about a month during the summer of 2011, which was treated with over the counter medication and then medications prescribed by the doctor, but she could not recall what the medication was. Tr. 16-17. Petitioner stated that she had had similar stuffy nose symptoms in the past, maybe once a year. Tr. 30-31. Mr. Giannetta recalled petitioner having a cold for a long time after receiving the Menactra vaccine. Tr. 37-38.

Dr. Mar suggested that petitioner had a "presumed viral illness" for three weeks in July of 2011 with coughing and congestion. Pet. Ex. A at 8. This statement was made in the context of Dr. Mar disputing the theory of molecular mimicry in Menactra triggering MS. But other than a

presumption, she pointed to nothing definitive in the record to confirm that petitioner had a viral illness and not simply allergies. *Id*.

Dr. Steinman referenced Dr. Patterson's and Dr. Rodriguez's notes from the Mayo Clinic, noting that they did not make any findings regarding petitioner's "cold-like" symptoms in July 2011. Tr. 126-27. Dr. Steinman placed no importance on these symptoms in petitioner's development of MS. Tr. 127. According to Dr. Steinman, there would be no way to know whether petitioner's symptoms were caused by a microbe or allergen. Tr. 130. Dr. Steinman stated that it would be "illogical" to place more weight on "cold-like" symptoms, which could be caused by allergies or a virus, rather than on a vaccine, which is a definite, known quantity. Tr. 130. Dr. Steinman stated that, if petitioner had had a fever it would have indicated that her symptoms were more likely due to an infection than an allergy. Tr. 131. Therefore, the presence of the "cold-like symptoms" in July of 2011 with nothing more did not change Dr. Steinman's opinion in this case. Tr. 131.

Whether a cold or allergies, there was nothing significant about petitioner's stuffy nose and cough in July of 2011, or any indication that she had a fever. Accordingly, respondent points to nothing in the record to indicate that these symptoms were of any import in petitioner's development of MS. Therefore, respondent has not met his burden of showing that an alternative cause was the sole substantial factor in causing petitioner's MS.

V. Conclusion

Accordingly, petitioner has put forth preponderant evidence that the Menactra vaccine she receive on June 8, 2011, triggered her development of MS. She has therefore demonstrated entitlement to compensation. This case shall proceed to damages.

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master